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Case Report

# A phase 1/2 open label nonrandomized clinical trial of intravenous 2-hydroxypropyl-β-cyclodextrin for acute liver disease in infants with Niemann-Pick C1

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ABSTRACT

*Introduction:* Niemann-Pick C (NPC) is an autosomal recessive disease due to defective NPC1 or NPC2 proteins resulting in *endo*-lysosomal storage of unesterified cholesterol in the central nervous system and liver. Acute liver disease in the newborn period may be self-limited or fatal. 2-hydroxypropyl-β-cyclodextrin (2HPBCD) is a cholesterol-binding agent that reduces lysosomal cholesterol storage. We have enrolled 3 infants 0–6 months old with direct hyperbilirubinemia due to NPC1 or NPC2 liver disease in a Phase I/II open label clinical trial of intravenous 2HPBCD.

*Methods:* Infants received intravenous 2HPBCD twice a week for 6 weeks, followed by monthly infusion for 6-months. Primary outcome measure was reduction of plasma (3β,5α,6β-trihydroxy-cholan-24-oyl) glycine (TCG), a bile acid generated from cholesterol sequestered in lysosome.

*Results:* Three participants completed this protocol. A fourth patient received intravenous 2HPBCD under an emergency investigational new drug study but later expired from her underlying condition. The three protocol patients are living and have improved liver enzymes and TCG. No patient has experienced a drug-related adverse event.

*Conclusion:* Intravenous 2HPBCD was tolerated in three infants with liver disease due to NPC.

## 1. Introduction

Niemann-Pick disease, type C (NPC) has an incidence of 1 in 120,000 live births. It results from pathogenic variant of either the *NPC1* (~95% of cases) or *NPC2* genes [1]. The NPC1 protein is a cholesterol trafficking protein, so the *NPC1* gene mutation results in accumulation of unesterified cholesterol and other lipids in lysosomes leading to disease involving the central nervous system and peripheral tissues such as the liver [1]. NPC has a phenotypic spectrum ranging from infantile death to a chronic neurodegenerative disease in adulthood. Most commonly, it is characterized by neurodegeneration in early childhood and death in adolescence [1]. Individuals with NPC demonstrate progressive central nervous system decline including inability to coordinate balance, gait, and extremity movements. Liver disease in the newborn/infant period is frequently observed. Some patients succumb to progressive liver disease, but in many patients the liver disease improves resulting in chronic liver disease [1].

There is currently no treatment for NPC in the United States, but clinical trials are ongoing with 2-hydroxypropyl-beta-cyclodextrin (2HPBCD). Here, we report our preliminary experience with intravenous 2HPBCD to treat the infantile liver disease in NPC patients. One subject, Patient A, was treated under an emergency investigational new drug (IND) study, and three have enrolled in a phase 1/2a, open-label, multiple ascending dose trial. The study aims to evaluate whether 2HPBCD administered intravenously may be safe and effective in treating liver disease in NPC infants.

## 2. Materials and methods

Studies were reviewed and approved by the Human Research

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Protection Office at Washington University in St. Louis School of Medicine in St. Louis, Missouri. It was approved by the Federal Drug Administration as an Investigational New Drug. All patients underwent written, informed consent for the trial and gave permission for inclusion in this report. 2HPBCD (Kleptose HPB) was formulated as VTS-270 (Mallinckrodt Pharmaceutical, Bedminster, NJ). Prior to the approval of the open-label clinical trial, a patient with NPC and liver failure presented to St. Louis Children's Hospital (SLCH), and was treated under an emergency IND.

### 2.1. Administration and dosing protocol

To be enrolled in the study, patients were required to be 0–6 months of age, carry a diagnosis of NPC1 or NPC2, and have a hyperbilirubinemia. VTS-270 was administered intravenously through a peripherally inserted central catheter placed (PICC) place after admission to the Neonatal Intensive Care Unit (NICU) at St. Louis Children's Hospital. VTS-270 was provided as a 200 mg/mL solution and administered at a rate of 250 mg/kg/h. Dosing for this phase one trial began at 500 mg/kg. The infusion rate was decreased in 25 mg/kg/h increments to 175 mg/kg/h if required.

Infants remained in the NICU for doses 1 and 2, on standard NICU continuous monitoring.

### 2.2. Doses 3–18

Interval between dosing was 4 ± 1 days. IV VTS-270 was administered via the central venous line at a rate of 250 mg/kg/h. Rate, vital signs (temperature, heart rate, respiratory rate, supine blood pressure, and $SaO_2$) and standard neurological checks were conducted as for dose 1 and 2. These doses were given as an outpatient, within our Pediatric Clinical Research Unit.

### 2.3. Modifications in the event of toxicity

If the subject did not tolerate the 500 mg/kg dose, the dose was to be decreased to 250 mg/kg. If the subject did not tolerate the 1000 mg/kg dose, the dose was to be decreased to 500 or 250 mg/kg.

### 2.4. Emergency IND modifications

The subject treated under the eIND was initiated at 250 mg/kg, and sequentially increased to 500 mg/kg, and 1000 mg/kg, when laboratory and clinical status did not improve.

### 2.5. Assessment of efficacy

Determination of efficacy was based upon biochemical response of plasma biomarkers (e.g., cholestane-3β,5α,6β-triol (C-triol) [2], 7-ketocholesterol (7-KC) [2], 3β,5α,6β-trihydroxy-cholan-24-oyl) glycine (TCG) [3], and N-palmitoyl-O-phosphocholine-serine (PPCS)) [4]; serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT) and total and direct bilirubin; and abdominal ultrasound to assess changes in liver and spleen volumes.

### 2.6. Open-label clinical trial

For subjects in Phase I of the study, infants were treated twice weekly for six weeks. After completion of Phase I, children were then evaluated for eligibility to progress to Phase II of the study in which they were treated once per month for six months.

Patients included in the study underwent the following laboratory tests:

#### 2.6.1. Hematology

complete blood count (CBC) with differential and platelet count, and prothrombin time (PT).

#### 2.6.2. Clinical chemistry

electrolytes, glucose, blood urea nitrogen (BUN), creatinine, AST, ALT, gamma-glutamyl transferase (GGT), alkaline phosphatase, bilirubin (direct and total), albumin, calcium, magnesium, phosphorus, total protein, and creatine kinase (CK).

#### 2.6.3. Urinalysis

protein, blood, leukocytes, glucose, ketones, bilirubin, urobilinogen, pH, and specific gravity and microscopic analysis.

In Phase I, testing occurred at baseline, 2, 4 and 6 weeks. In Phase II, testing occurred at baseline, 2, 4, and 6 months.

Patients also underwent additional research testing of NPC1 specific markers including TCG (ref < 13.5 ng/mL), C-triol (ref <0.07 ng/mL), 7-KC (ref <0.10 ng/mL), PPCS (ref <0.10 ng/mL) (Phase I: Baseline, 2, 4 and 6 weeks; Phase II: Baseline, 2, 4 and 6 months.).

Additional testing for the study included:

**In Phase I:** audiological evaluation, specifically, otoacoustic emissions (OAE) without sedation (baseline, 6 weeks)

Abdominal ultrasound (baseline, 6 weeks) Liver size was determined by the liver's midclavicular longitudinal diameter. Organ volumes are the product of three long axes (longitudinal, transverse and anterior-posterior).

**In Phase II:** abdominal ultrasound (6 months)

Subjects who demonstrated reduction either in TCG or serum bilirubin (direct bilirubin or direct bilirubin:total bilirubin ratio) were eligible to enter into the second Phase of the study, an open-label Phase of six months duration in which IV 2HPBCD was administered monthly for a total of six doses. Procedures during the second Phase included a monthly intravenous line placement, physical assessment, blood draws and urine collection during month 1, 2, 4, and 6, and monthly drug administration.

Primary outcome measure is the efficacy of IV 2HPBCD to reduce plasma levels of TCG. Secondary outcome measures include: effect of drug on serum transaminases (ALT, AST) and reduction of liver and/or spleen volumes.

## 3. Results

The study has enrolled three subjects, and none have withdrawn. One additional patient was treated under an eIND for acute liver failure before the study opened for enrollment. This patient, Patient A, expired from her liver disease.

### 3.1. Patient A

A 38 3/7 weeks post menstrual age (PMA) female born at 2.63 kg (Table 1) with birth history significant for intrauterine growth restriction, delayed prenatal care (21 weeks) due to lack of health insurance, and family history of a "close" relative with a child who died at 2 months of age due to unclear reasons including hepatic failure. Patient A presented with cholestasis and hepatosplenomegaly (Fig. 1) at <1 week of age. Coagulation studies were abnormal. Abdominal ultrasound confirmed splenomegaly and revealed a coarse liver, loss of the uniform smooth echotexture, with a cavernous hemangioma. Alpha fetoprotein (AFP) was elevated at 77,000 ng/mL with repeat value of 92,000 (nl <41,687 ng/mL). Sequencing of *NPC1* revealed a likely pathogenic variant designated as c. 3053 G > A;p.C1168Y [5] and a variant of uncertain significance (VUS) designated as c.1301C > G; p.P434R [6].

The Phase 1/2 clinical trial had not yet opened for enrollment, so a single patient emergency treatment was pursued for this baby. At 6 weeks of life, she underwent her first infusion of 2HPBCD. At 6 weeks old prior to initiation of the treatment, the child had hepatosplenomegaly, end stage liver disease, ascites, direct hyperbilirubinemia, elevated liver enzymes, hypoalbuminemia, and

**Table 1**
Demographics, genotype, and clinical summary of NPC patients.

| | Patient A | | Participant 1 | | Participant 2 | | Participant 3 | |
|---|---|---|---|---|---|---|---|---|
| Demographics | | | | | | | | |
| Sex | Female | | Male | | Male | | Male | |
| Race/Ethnicity | Southeast Asian | | White/Hispanic | | White/Hispanic | | White | |
| Estimated gestational age | 38 3/7 weeks | | 39 weeks | | 33 6/7 weeks | | 33 3/7 weeks | |
| Birth weight | 2630 g | | 2899 g | | 2495 g | | 2125 g | |
| Birth length | 47.1 cm | | 50 cm | | 45.5 cm | | 45 cm | |
| Occipitofrontal circumference | 32 cm | | 34 cm | | 31.5 cm | | 30 cm | |
| Age at study enrollment | Shortly after birth | | 4 months old | | 2 months old | | 5 months old | |
| Genetic information | | | | | | | | |
| *NPC1*cDNA change | c.3503G > A | c.1301C > G | c.2621A > T | c.3557G > A | c.2872C > T | c.451_452del | c.332dupG | c.1210C > T |
| Protein change | p.C1168Y | p.P434R | p.D874V | p.R1186H | p.R958X | p.S151FfsX18 | p. A1108RfsX13 | p.R404W |
| Mutation types | Likely pathogenic | VUS | Pathogenic | Pathogenic | Pathogenic | Pathogenic | Pathogenic | Likely pathogenic |
| Inheritance | Not tested | | Maternally-inherited | Paternally-inherited | Maternally-inherited | Paternally-inherited | Not tested | |
| Method of detection | Cholestasis gene panel | | Parental carrier screening, targeted gene sequencing | | Whole genome sequencing | | Cholestasis gene panel | |
| Clinical information | | | | | | | | |
| Abdominal ascites | + | | + fetal | | – | | – | |
| Neonatal jaundice | + | | + | | + | | + | |
| Hepatomegaly | + | | + | | + | | + | |
| Splenomegaly | + | | + | | + | | – | |
| Vertical supranuclear gaze palsy | – | | – | | + | | – | |

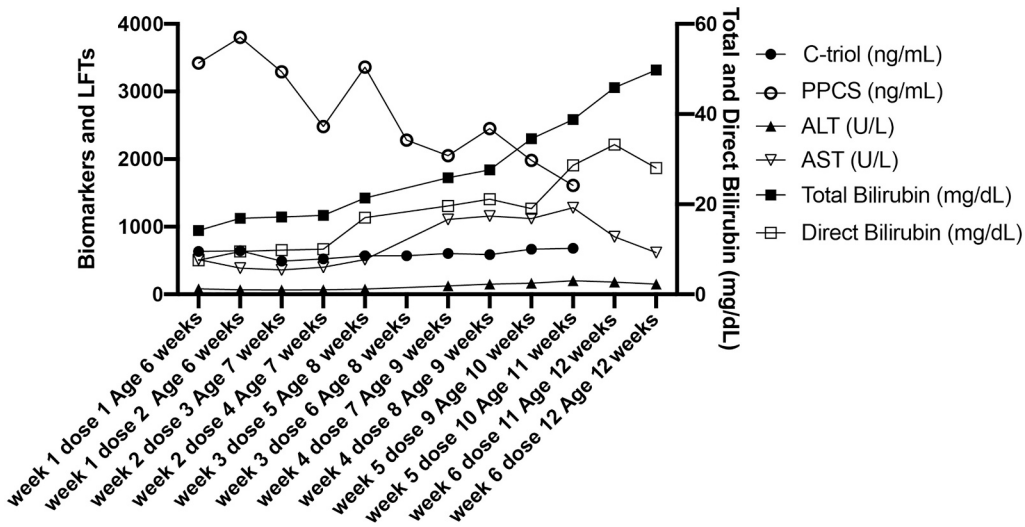


**Fig. 1.** Biomarkers, liver function tests (LFTs) and bilirubin concentrations in Patient A. C-triol: cholestane-3β,5α,6β-triol C-triol. PPCS: N-palmitoyl-O-phosphocholineserine.

pancytopenia. Her multiple abdominal ultrasounds prior to treatment revealed multiple and increasing hypoechoic liver lesions increasing, hepatosplenomegaly, ascites, and edematous bowel. Doppler studies did not document portal hypertension prior to treatment. She tolerated doses at 250 mg/kg, 500 mg/kg, and 1000 mg/kg without adverse events. The doses were escalated as she tolerated the medication, and her systemic condition worsened. She completed 12 infusions of 2HPBCD. Her PPCS decreased from 3420 to 1610 (Fig. 1). Downtrending of PPCS, which has been used as a marker for NPC severity, has been previously been shown to decrease with IV 2HPBCD and potentially indicates a reduction of lipid in the liver [2,7,8]. Unfortunately, the patient expired prior to undergoing monthly infusions due to end stage liver disease that was unrelated to drug administration (Fig. 1, Supplementary Table 1).

### 3.2. Study participant 1

The first study subject received a prenatal diagnosis of NPC1. Fetal ascites was noted at the 24-week ultrasound. DNA extracted from amniotic fluid revealed that the patient was compound heterozygous for two pathogenic variants, one maternally inherited (c.2621A > T, p. D874V) [9] and the other paternally inherited (c.3557G > A, p. R1186H). The patient was born at 39 weeks (Table 1) and admitted to the NICU post-delivery. Phototherapy was initiated for hyperbilirubinemia. (Fig. 2a, Supplementary Table 2).

The study was first contacted when he was 4 months of age. Physical examination showed hepatosplenomegaly. Abdominal ultrasound revealed cirrhosis and a hyperechoic lesion within segment 4, which was thought to represent a cholesterol deposit. AFP was elevated at 23,135

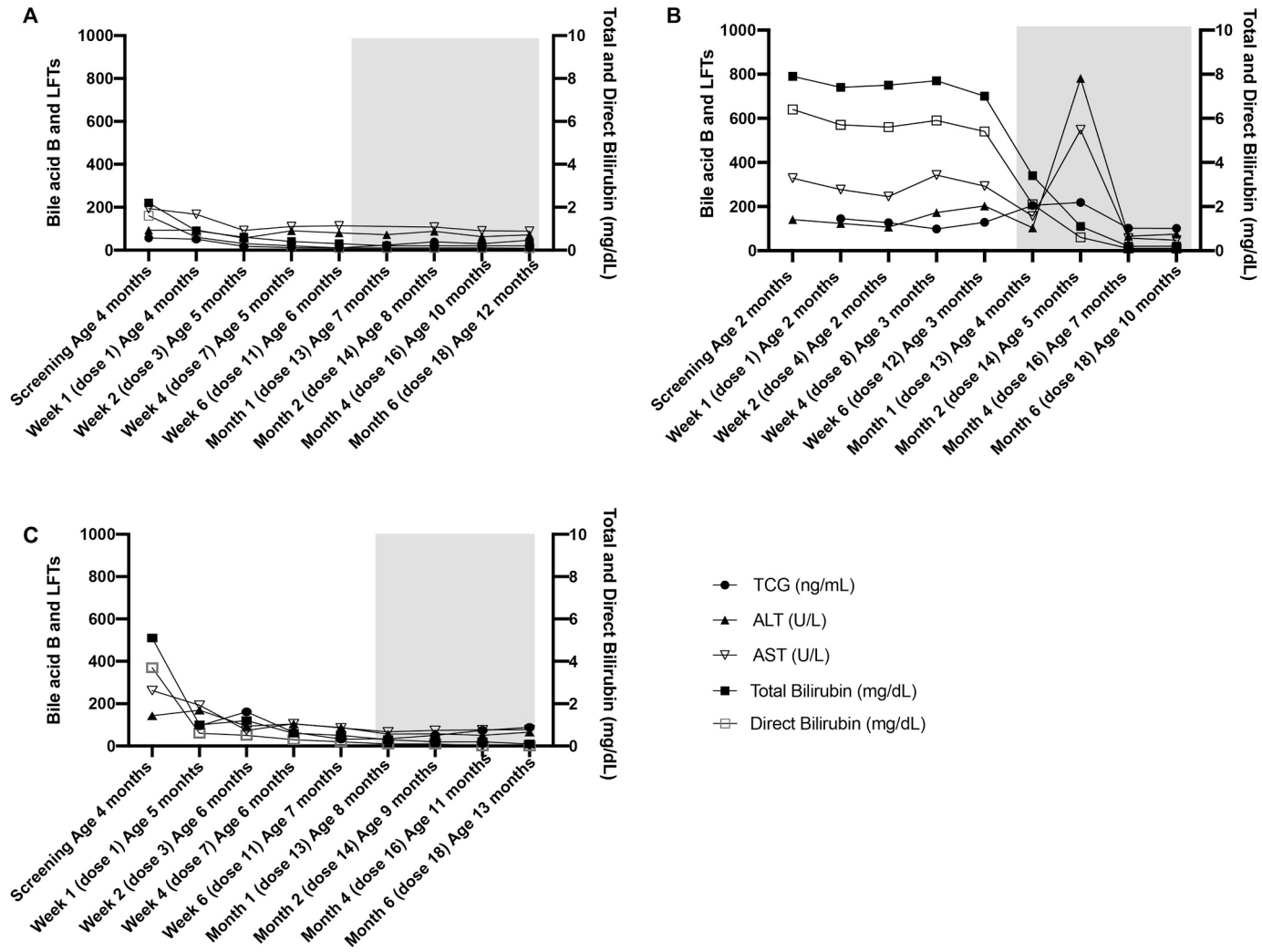


**Fig. 2.** Biomarkers, liver function tests (LFTs) and bilirubin concentrations in clinical trial subjects. A) Study participant 1; B) Study participant 2; C) Study participant 3. Gray shading indicates second phase of the study, when dosing frequency changed from twice weekly (approximately every four days) to once monthly. TCG: 3β,5α,6β-trihydroxycholan-24-oyl glycine. Study participant 2 experienced an acute change in liver function studies at month 2 (dose 14) which corresponded temporally with a viral infection. Scale of y-axis differs between Figs. 1 and 2.

ng/mL (nl 8-87 ng/mL). He was started on IV 2HPBCD per study protocol at age 4 months. A repeat AFP level at 6 months demonstrated downward trending levels to 1171 ng/mL. Direct bilirubin decreased to 0.3 mg/dL (nl 0.1–0.3) two weeks after his first infusion and remained within normal limits after the 6-week infusion completing the first phase of the protocol (Fig. 2, Supplementary Table 2). He met criteria to transition to the second Phase of the study and was treated monthly with IV 2HPBCD for six months. At the end of the study, his AST and ALT improved but remained elevated. His bile acid marker was similarly improved but elevated.

The liver size at the end of the study by ultrasound was 8.7 cm, which was improved from initiation of the study. (Table 2) Finally, OAE remained within normal limits for the duration of the study.

### 3.3. Study participant 2

The second study participant was a male infant born at 33 6/7 weeks gestational age. Pregnancy was complicated by preterm labor and breech presentation. He was delivered by C-section with a birth weight of 2.495 kg (Table 1). The patient was admitted to the NICU for three weeks due to poor weight gain and persistent elevated bilirubin and liver transaminases. (Fig. 2b., Supplementary Table 3) Whole genome sequencing revealed that the patient was compound heterozygous for two pathogenic variants in *NPC1*, one maternally inherited (c.2872C > T, p.Arg958Ter) and the other paternally inherited (c.451_452del, p. Ser151PhefsTer18)e.

The study was first contacted when he was 2 months old. This patient initiated study treatment at age 2 months of age and completed Phase I of the protocol receiving two infusions of IV 2HPBCD per week for 6 weeks. After Phase I his liver function studies showed improvement (Fig. 2b, Supplementary Table 3). After completion of the monthly infusions, his AST remained somewhat elevated at 75 units/L (nl 10–60 units/L) and ALT 48 units/L (nl 5–50 units/L). His bile acid B was 101 ng/mL. His liver by ultrasound measured 8.10 cm which was improved from baseline at the initiation of the study (Supplementary Table 5) The participant's OAE remained unchanged for the duration of the study.

### 3.4. Study participant 3

The third study participant was a 5-month-old boy born at 33 3/7 weeks post-menstrual age due to preterm labor. His birthweight was 2125 g. He developed jaundice in the NICU which provoked a workup. Genetic testing showed two heterozygous variants of NPC1: c.3320dupG (p.A1109RfsX13 and a c.1210C > T (p.R404W) that were classified as

**Table 2**
Abdominal ultrasound reports.

| Patient A | | | |
|---|---|---|---|
| | Baseline | | End treatment[a] |
| Spleen size | 6.90 cm | | 9.00 cm |
| Liver size | 7.10 cm | | 10.00 cm |
| Body weight | 2.60 kg | | 4.00 kg |
| Body length | 51.5 cm | | 54.0 cm |
| **Study Subject 1: VTS-270-WU01** | | | |
| | Baseline | End phase 1 | End phase 2 |
| Spleen size | 8.56 cm | 9.00 cm | 10.4 cm |
| Spleen volume | 88.4 cc | 98.1 cc | 177.2 cc |
| Liver size | 9.55 cm | 9.60 cm | 8.7 cm |
| Body weight | 6.97 kg | 7.90 kg | 11.6 kg |
| Body length | 67.0 cm | 69.8 cm | 78.2 cm |
| **Study Subject 2: VTS-270-WU02** | | | |
| | Baseline | End phase 1 | End phase 2 |
| Spleen size | 7.96 cm | 8.40 cm | 11.20 cm |
| Spleen volume | 84.2 cc | 71.8 cc | 127.0 cc |
| Liver size | 8.83 cm | 8.70 cm | 8.10 cm |
| Body weight | 3.33 kg | 4.40 kg | 8.60 kg |
| Body length | 50.5 cm | 54.5 cm | 72.8 cm |
| **Study Subject 3: VTS-270-WU03** | | | |
| | Baseline | End phase 1 | End phase 2 |
| Spleen size | 6.70 cm | 7.10 cm | 7.60 cm |
| Spleen volume | 67.0 cc | 58.6 cc | 69.2 cc |
| Liver size | 9.00 cm | 8.30 cm | 10.00 cm |
| Body weight | 5.78 kg | 7.10 kg | 9.20 kg |
| Body length | 61.5 cm | 62.4 cm | 72.7 cm |

[a] Measured by abdominal MRI.

likely pathogenic. 7-KC was elevated at 1.446 nmol/mL (ref <0.10), C-triol was elevated at 0.300 nmol/L (ref <0.07), and PPCS was within normal limits at 0.010 nmol/mL (ref <0.10). The oxysterol profile is consistent with a biochemical diagnosis of NPC.

The study was first contacted about this patient when he was 4 months old. He presented 1 month later (Fig. 2c, Supplementary Table 4) and initiated the study drug at age 5 months. After Phase I his lab values improved. His liver was 8.3 cm, which was decreased from baseline 9.0 cm. After completion of the monthly infusions, his AST remained somewhat elevated at 77 units/L (nl 10–60 units/L) and ALT 65 units/L (nl 5–50 units/L). His final bile acid B was 87.9. His liver by ultrasound measured 10 cm (Supplementary Table 5). The participant's OAE remained unchanged for the duration of the study.

### 3.5. Subjects not enrolled

Twelve additional children were pre-screened for enrollment. Four children did not meet inclusion criteria: one was excluded based on age (10 years old), and three were excluded because they did not have liver disease. Two children received off-site drug via an eIND: one because the study had not yet opened for enrollment, and one because the child was too unstable to travel. Two children were in critical condition and succumbed to their illness prior to traveling to our institution or receiving treatment. Finally, four children contacted the study team, but after conversations with the team, families opted not to participate in the study. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic was a factor in the decision not to travel to St. Louis for the study for two of these four potential participants.

### 3.6. Adverse events

Patients have not had adverse events related to the study drug. Adverse events occurring during the study have included PICC line erythema, elevated transaminases, fever, cough, and viral exanthem.

## 4. Discussion

Four patients with NPC1 have received IV 2HPBCD at our institution. Three patients are alive and had improvement in TCG and their liver function studies, and bilirubin levels during the course of study participation. Neonatal liver disease typically resolves in infants with NPC1 who survive the acute phase, so it is difficult to determine whether IV 2HPBCD impacted the natural disease course. This study was limited by a lack of control group due to concerns at the time that this would be practically and ethically challenging.

*NPC1* encodes a large membrane glycoprotein, which localizes to the late endosome [10]. *NPC2* encodes a small soluble lysosomal protein that binds cholesterol. Both proteins are found in the late endosomal/lysosomal (LE/LY) system. NPC1 and NPC2 protein are thought to facilitate egress of cholesterol from LE/LY to other parts of the cell [11]. This accumulation of cholesterol then results in glycosphingolipid accumulation [12]. These mutations lead to impairment in processing and utilizing cholesterol causing cholesterol storage and alterations of sphingomyelin metabolism in extra neural tissues [1]. The result of NPC1 and NPC2 mutations is that cholesterol does not exit the endocytic pathway but accumulates within lysosomes.

This accumulation causes half of patients to experience prolonged neonatal cholestatic icterus and progressive hepatosplenomegaly [9,13]. In most cases, the icterus spontaneously improves, but the hepatosplenomegaly may persist. Among 10% of patients, the icterus quickly worsens, and the patients develop liver failure. These patients typically die before the age of 6 months.[12] We cannot yet predict which patients will recover from their liver disease versus which patients will progress to liver failure [9]. Of the patients who survive liver failure, all eventually experience progressive and fatal neurologic disease [14]. Classic neurologic symptoms include cerebellar ataxia, dysarthria, dysphagia, dementia, and vertical supranuclear gaze palsy [14].

A study using intrathecal 2HPBCD/VTS-270 administration for NPC1 patients found that monthly 2HPBCD in 14 patients with NPC had decreased disease progression compared to matched natural history cohorts.[15] Seven patients experienced no progression or mild improvement, while all patients included in a natural history cohort progressed over 18 months [15].

The natural history of NPC has been studied. On review of 52 NPC patients, 34 (65%) had liver disease. In this study, 3 infants had a progressive course during infancy which led to their demise, 4 had progressive liver disease, while 15 had mild persistent liver disease [9]. Similarly, in another review of patients in the UK with NPC, 47 of 94 patients had neonatal presentation, 4 of these patients died before age 1 [5]. A study from the same group in 2015 found that the severe neonatal onset form of NPC was most commonly associated with death from liver disease in 3 of 6 patients.[13] In a NPC database, 87/136 patients returned a questionnaire, and 52% reported neonatal jaundice with splenomegaly (35%), hepatomegaly (31%) and ascites (19%). In our cohort, patient A had evidence of progressive liver disease, and died in infancy. While PPCS decreased in this baby after treatment, all biomarkers remained very high, and the child ultimately progressed to liver failure and death. All three infants (patients 1–3) enrolled in our study have mild persistent liver disease. None of these infants have evidence of progressive liver disease. On the contrary, there was an improvement in cholestasis in all three infants and hepatomegaly (liver size on ultrasound) in all three infants enrolled in our study. In addition, there were no signs indicating development of portal hypertension or ascites on ultrasound or duplex studies. The clinical significance of the persistent liver disease in NPC is usually overshadowed by the development of severe neurologic disease.

In the aforementioned study, liver disease did not correlate with the onset of neurologic disease, which starts at mean of 4.5 years [16]. We did see an increase in splenomegaly in all three infants in our study [17].

The exact mechanism of 2HPBCD's effect is unknown. One theory is that 2HPBCD reaches the LE/LY system and can facilitate movement of stored cholesterol. It is believed that 2HPBCD can replace NPC1 or NPC2 or it may complex with other proteins and cause cholesterol flux in other ways, e.g. promoting autophagic flux [18]. In so doing, it may lead to normalized trafficking and clearance of accumulated cholesterol and glycosphingolipids [19–21].

Because NPC is a cholesterol storage disorder, it results in an accumulation of cholesterols. The most important plasma biomarkers for NPC include oxysterols (C-triol and 7-KC), TCG, and PPCS, all of which are significantly elevated in NPC. However, we do not know how any of these markers change over time. Oxysterols are generated from cholesterol trapped in lysosome due to oxidative stress, and TGC is a metabolite of C-triol. The biosynthesis of PPCs is unknown, and it is very likely that its elevation is secondary to accumulation of cholesterol in lysosome. Cholesterol is significantly elevated in liver in NPC disease, and liver is a major organ to produce oxysterols and TCG. Clearance of accumulated cholesterol in lysosome of liver by 2HPBCD leads to decrease of these NPC biomarkers [4]. Finally, 3 beta, 5 alpha, 6 beta-trihydroxycholanic acid (bile acid B) is a metabolite of oysterol cholestane-3 beta,5 alpha,6 beta-triol (COT) and is elevated in NPC. Our group developed the bile acid B screening as a more suitable way to screen infants for possible NPC using dried blood spots [22]. This assay is now being piloted as a newborn screen in NY State.

In summary, three patients have been enrolled in this open-label Phase I/II clinical trial for infants with liver disease due to NPC. One additional patient was treated with an emergency IND, but succumbed to liver disease. No patient has had significant adverse events related to the drug. At last follow up, all surviving patients had TCG, a marker of cholesterol storage, improved from the initial visit. Liver transaminases improved all subjects. Liver size decreased in all subjects. Additional subject accrual and study are needed to determine whether neonatal liver disease due to NPC may improve during treatment with 2HPBCD.

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Mallinckrodt provided the drug.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2021.100772.

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